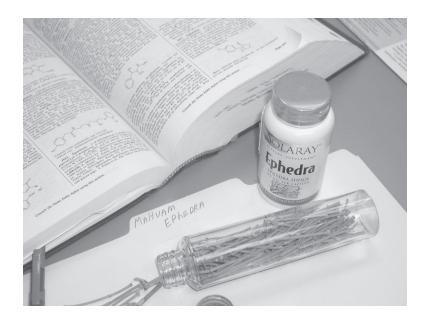
Addressing the Potential Risks Associated with Ephedra Use: A Review of Recent Efforts

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SYNOPSIS

The appropriate amount of oversight for dietary supplements has been a subject of debate for over a decade. This debate has come to a head recently with herbal ephedra, which may be associated with adverse events including heart attack, stroke, seizure, and death. This article reviews and puts into



context recent findings on the safety concerns related to ephedra, based primarily on adverse event reports. It presents the response from industry and the FDA in light of this evidence, and describes additional steps taken by other groups who believe that more restrictive action is required. The article concludes by observing the lack of explicit, shared criteria for determining whether a supplement is unsafe, and pointing out ways in which the experience with ephedra can be used constructively to address that problem.

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As a class of products and sometimes individually, dietary supplements have generated significant debate within the regulatory community for over a decade.¹ Millions of people use dietary supplements—vitamins, minerals, herbs and botanical extracts, and amino acids—to enhance their diets and promote their wellbeing. Approximately 150 million consumers (70% of the U.S. population) used supplements to some degree in 2001; 80 million (36% of the U.S. population) were regular or heavy users.² About 175 different types of supplements are on the market today, and many are readily available through grocery stores and drug stores.³

Dietary supplements are classified as a type of food under the Dietary Supplement Health and Education Act of 1994 (DSHEA), which also lays out the Food and Drug Administration's (FDA) authority to regulate these products. Because of their classification, supplements need not undergo formal safety and efficacy testing before being marketed. As a result, the way in which a supplement affects the body—both its effectiveness in doing what it claims and possible side effects or interactions—may not be fully researched when consumers purchase and use it. Consumers, however, may not be aware of this.⁴

The supplement industry maintains that dietary supplements as a whole are safe, and that the current level of oversight is effective.⁵ Industry advocates emphasize that most consumers use supplements without problems, and that FDA has the authority to enforce good manufacturing practices and accurate labeling, and to monitor supplement safety through its adverse event reporting system. Further, under DSHEA, the FDA can remove from the market any supplement that poses a "significant or unreasonable risk of illness or injury."⁶

On the other side of the debate, consumer protection groups contend that the current approach to supplement regulation leaves consumers at too much risk.⁷ They point out that the FDA's adverse event reporting system is voluntary, and that it receives information about only a small fraction of problems that consumers experience. They further maintain that the burden of proof required of the FDA to remove a potentially dangerous supplement from the market is too great.

The case of ephedra highlights the tension between the two sides. Studies of reported adverse events have raised concerns that ephedra may be associated with heart attacks, seizures, stroke, and death, as well as nausea, vomiting, anxiety, hypertension, tremors, and palpitations, but the FDA has determined that the current level of evidence is not sufficient to support a ban under the conditions laid out in DSHEA. Both the FDA and industry have issued warnings to alert consumers about the possible risks associated with ephedra use. But given the severity of these potential safety problems, combined with the limited evidence of ephedra's effectiveness, there has been widespread sentiment that more stringent measures are appropriate. This has resulted in several states, counties, retailers, and independent associations issuing their own restrictions on ephedra, as well as heated calls for a national ban from advocacy and medical organizations.

This article summarizes recent developments in the oversight of ephedra, and uses this example as a case study to point out the need for further clarification of the standards upon which the decision to restrict or ban the sale of a dietary supplement should be based.

CAUSE FOR CONCERN

Ephedra is a desert plant whose extract is used in traditional medicine to treat asthma and other respiratory conditions; it has been sold in the United States to stimulate weight loss and boost athletic performance. An estimated 12 million people used ephedra in 1999, the most recent year for which statistics are available. In that time, the industry reported sales of about three billion servings. 9

A recent meta-analysis of controlled trials of ephedra and ephedrine alkaloids (known as the RAND study) found that the substance had modest short-term effects and unknown long-term effects on weight loss. The reviewers could not determine the extent to which ephedra enhanced athletic performance, due to insufficient evidence.¹⁰

The death of Baltimore Orioles' pitcher Steve Bechler in February 2003 propelled concerns related to ephedra use into the national spotlight. Bechler's body temperature rose to 108 degrees during a spring training workout, a few hours after he took a large dose of a supplement that contained ephedra. A toxicology report found that ephedra toxicity "played a significant role" in his death. He was 23 years old.

Although Bechler's untimely death generated more national media attention than other cases, evidence of the potential risks of ephedra use has been mounting for years. From February 1993 through July 2003, FDA's adverse event reporting system documented 2,277 adverse events among ephedra users. These numbers are probably very conservative estimates, since a report commissioned by the FDA in 2000 concluded that the system likely received only 1% of the adverse events related to dietary supplements. The FDA has since revised its adverse event reporting system for

supplements.) More accurate data may come from the American Association of Poison Control Centers (AAPCC), which in 2002 alone received reports of 1,428 adverse events among ephedra users. ¹² In addition, an investigation of Metabolife International, a major manufacturer of products containing ephedra, found records of 14,684 reports of ephedra-related adverse events from May 1997 through July 2002. ¹⁴ The reported adverse events include death, heart attack, stroke, seizure, nausea, vomiting, anxiety, hypertension, tremors, and palpitations.

Case reports are limited in that they cannot in and of themselves confirm a causal association between ephedra exposure and these adverse events. Yet case reports are the major source of information about supplement safety, and there are generally accepted ways to use such observational data to draw inferences. In particular, case reports can be used to support the presence of an association based on a series of epidemiological criteria for causality:¹⁵

- Temporality, or whether the exposure and outcome are time-dependent;
- Specificity, or whether the outcome occurs from that one exposure and the exposure leads to that one outcome;
- Biological plausibility, or whether the association between the exposure and outcome makes sense from a physiological standpoint;
- Strength, or whether the association between the exposure and outcome is large and statistically significant;
- Consistency, or whether the association is supported across multiple studies with different populations;
- Gradient, or whether the dose of the exposure affects the likelihood and severity of the outcome.

The more criteria the case reports meet, the greater the likelihood of a causal association between the exposure and outcome. Independent reviews of the ephedra case reports appear to demonstrate that the association between ephedra and these adverse events meet at least three of the above criteria.

First, the association seems to be time-dependent. Samenuk et al. reviewed 926 cases of ephedra toxicity in FDA's adverse event reporting system from January 1995 through January 1997 and found a temporal relationship between ephedra use and the 37 reported cases of stroke, heart attack, and death. Not only did ephedra intake precede each of these events, but the duration of exposure also affected the likelihood of an adverse outcome. Eighty-nine percent of the events

occurred among people who had been taking ephedra for more than one week, and 73% occurred among people who had been taking ephedra for more than one month.¹⁶

Second, the association seems to be specific to ephedra compared to other dietary supplements; these adverse events are associated with ephedra exposure much more often than with the use of other dietary supplements. The number of adverse event reports FDA received for ephedra from February 1993 through July 2003 was more than 15 times the number of reports the agency received for any other supplement.¹² Moreover, an analysis by FDA officials of the agency's dietary supplement adverse event reports from January 1993 through February 2001 determined that ephedra-related cases represented 59% of all reported supplement-related deaths, 74% of reported supplement-related cardiovascular events, and 58% of reported supplement-related seizures.¹⁷ Further, Bent et al. disclosed that in 2001, the 1,178 ephedra-related cases reported to the AAPCC represented 64% of its documented adverse events for botanical products, even though ephedra accounted for less than 5% of sales of botanicals during that time.18

Third, the association seems to be biologically plausible. Haller and Benowitz rated each case of reported ephedra toxicity in the FDA's adverse event reporting system from June 1, 1997, through March 31, 1999, by likelihood of causation. They found that 31% of the reports were "definitely or probably" related to ephedra use; another 31% were "possibly" related. ¹⁹ As part of the RAND study, Shakelle et al. reviewed 284 case reports of serious adverse events from the FDA, Metabolife, and published studies that contained sufficient documentation to determine cause; they reported 22 "sentinel events" and 47 "possible sentinel events" in which ephedra use appeared to be associated with the adverse outcomes. ¹⁰

Many ephedra manufacturers continue to defend the supplement's safety profile, insisting that ephedra is safe when taken at the recommended dose. For example, a review conducted on behalf of the Ephedra Education Council, an industry supported group, determined that the association between ephedra exposure and heart attack, stroke, and seizure could not be supported among users who followed manufacturers' dosing guidelines, since the author's estimated incidence rates for those users seemed to parallel the underlying rates in the population.²⁰

However, consumers may have trouble following manufacturers' dosing guidelines. The Office of Inspector General recently reported that supplement labels are often unclear and/or provide insufficient information with regard to daily dose, maximum dose, and duration of use. ²¹ Further, when Gurley et al. tested 20 supplements that contained ephedra, they found that the actual amount of ephedra alkaloid per dose ranged from 0% to 150% of the amount declared on the label. ²²

WARNING STATEMENTS

Industry has long been aware of the potential risk of adverse events associated with ephedra use, and has promoted self-regulation among manufacturers. All of the supplement trade associations have adopted guidelines for their members to include a warning statement on the labels of supplements that contain ephedra, with the following information:

WARNING: Not intended for use by anyone under the age of 18. Do not use this product if you are pregnant or nursing. Consult a health care professional before using this product if you have heart disease, thyroid disease, diabetes, high blood pressure, depression or other psychiatric condition, glaucoma, difficulty in urinating, prostate enlargement, or seizure disorder, if you are using a monoamine oxidase inhibitor (MAOI) or any other prescription drug, or if you are using an over-the-counter drug containing ephedrine, pseudoephedrine or phenylpropanolamine (ingredients found in certain allergy, asthma, cough/cold and weight control products).

Exceeding recommended serving will not improve results and may cause serious adverse health effects.

Discontinue use and call a health care professional immediately if you experience rapid heartbeat, dizziness, severe headache, shortness of breath, or similar symptoms.²³

Industry first advocated such a warning in 1994. Several states soon followed suit, mandating that supplement manufacturers include the industry warning (or similar language) on the labels of all ephedra products sold in their states. Ohio first required this language in 1996; since then, Texas, Hawaii, Michigan, Nebraska, Washington, Oklahoma, and California have adopted similar regulations.

In February 2003, the FDA announced its intention to require the following mandatory warning statement on all ephedra supplement labels:

WARNING: Contains ephedrine alkaloids. Heart attack, stroke, seizure, and death have been reported after consumption of ephedrine alkaloids. Not for pregnant or breast-feeding women or persons under 18. Risk of injury can increase with dose or if used during strenuous exercise or with other products containing stimu-

lants (including caffeine). Do not use with certain medications or if you have certain health conditions. Stop use and contact a doctor if side effects occur. See more information \dots ²⁴

The proposed warning would appear in a black box on the front panel of the package. Additional information about product interactions, contraindications, and possible side effects would appear either on the package or in literature provided at the point of purchase. The FDA had originally proposed this measure in 1997, but was compelled to withdraw its plan after the General Accounting Office found that the agency did not have enough evidence to support such restrictions on ephedra.

RESTRICTIONS ON SALES

The FDA is contemplating stronger action against ephedra, and has asked health professionals, manufacturers, and the public to send in additional information about possible risks related to ephedra use so that the agency can conduct a more thorough assessment of the supplement's safety.²⁴ In the meantime, several groups have gone beyond FDA in restricting ephedra sales.

Suffolk County, New York, became the first U.S. government entity to ban all sales of ephedra in March 2003, followed by the state of Illinois, and Westchester and Rockland counties in New York. (Outside of the U.S., Canada requested a recall of ephedra products in 2002.) Massachusetts, California, and New York have bills under consideration to ban ephedra. California has already passed legislation declaring the sale of products that contain ephedra to anyone under the age of 18 to be a misdemeanor. (Florida has also banned the sale of all diet pills to anyone under the age of 18.) Ephedra use among young people is of particular concern because young athletes might overdose on ephedra products in an attempt to enhance their energy, speed, and stamina, and teenagers might abuse ephedra products to experience their amphetamine-like effects at high doses.

Ephedra use is no longer allowed among athletes who are part of the National Collegiate Athletic Association, the International Olympic Committee, the National Football League, Major League Soccer, and Minor League Baseball. Following Bechler's death, Major League Baseball announced that it was also considering a ban.

The American Medical Association, the American Heart Association, and consumer advocacy groups Consumers' Union and Public Citizen have petitioned

FDA to ban ephedra sales nationwide. Public pressure may create a de facto ban even without regulation. Several dietary supplement manufacturers have announced that they will stop production of supplements containing ephedra because of liability concerns, and have developed "ephedra-free" lines of their products. General Nutrition Centers, Eckerd and CVS drug stores, and 7-Eleven no longer carry ephedra products on their shelves. Ephedra products are also no longer available at military commissaries.

LEARNING FROM THESE APPROACHES

There is clearly a lack of consensus among groups with a stake in supplement oversight regarding the amount and type of evidence that is necessary to justify restrictions on the sale and use of ephedra. This raises some larger questions: To what extent should the magnitude of use of a supplement play a role in the decision to restrict its sales when a safety concern arises? What about the severity of the reported events? Is it appropriate to issue restrictions for vulnerable populations (such as young people) with less evidence than would be required for banning the supplement altogether? Do consumers heed warning statements enough to make them an effective regulatory tool for supplements?

These issues are at the core of monitoring supplement safety under the current regulatory framework. The experience with ephedra can provide the most substantive insights to date about these issues. This case not only illustrates the extent to which such points are still unclear, undecided, or problematic, but also offers a set of potential answers through the various approaches that different groups have taken. Regulators, industry associations, and other groups that have implemented or advocated for additional oversight should be encouraged to make their stances on these points more explicit, in order to justify any additional steps to restrict ephedra use, to help the public put current reports about concerns with ephedra's safety into perspective, and to establish criteria that can be used to address in a proactive and concerted manner any future situations in which a dietary supplement poses a safety concern.

The views expressed in this article are those of the author and do not reflect those of the Department of Health and Human Services or the Office of the Inspector General.

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